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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/999,690	09/08/1997	WALTER H. GUNZBURG	GSF97-03A	4218

21005 7590 02/25/2004

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/999,690	GUNZBURG ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/20/03* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-15,20-22,26-28,30,31,34-40,46-48,52,55-65,70-72 and 75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-15,20-22,26-28,30,31,34-40,46-48,52,55-65,70-72 and 75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 May 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment and remarks filed on November 20, 2003 has been entered. Claims 1, 2, 5-8, 21, 27, 28, 30, 31, 34, 55-59 have been amended, and claims 16-19, 23, 25, 42-45, 49, 53, 54, 66-69, 73, 74, 76, 77 have been canceled. Claims 1, 2, 4-15, 20-22, 26-28, 30, 31, 34-40, 46-48, 52, 55-65, 70-72, 75 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

WRITTEN DESCRIPTION

The prior rejection of claims 1, 2, 4, 5-8, 21, 27, 28, 30, 31, 34, 55-59 under 35 U.S.C. 112, first paragraph, is withdrawn in view of claim amendment limiting the vector to retroviral vectors.

However, previous rejection under this section with respect to claim recitations, "a biologically active derivative" of an antimicrobial peptide, "a part thereof, an analogue thereof, and a homologue thereof", has been reinstated, and applies to pending claims 1, 2, 4-15, 20-22, 26-28, 30, 31, 34-40, 46-48, 52, 55-65, 70-72, 75.

In view of the disclosure of the original specification, it teaches a few art known analogues for melittin and cecropin, such as those detailed in page 4 and 9 of the specification, however, the claims are much more broader than what is discussed in the specification.

As a genus, melittin and cecropin are known to be lytic peptides and certain residues may be associated with its membrane binding activity and other residues are essential for lytic activity (*Rivett et al.* Biochem J 1996; 316:525-29). Early studies have been focused on its secondary structural and functional relations in heomlytic activities (*Perez-Paya et al.*Biochem J 1994 Apr;299:587-91), catalytic activities (*Perez-Paya et al.* Pept Res 1994 7:286-8), and its surface properties (*Perez-Paya et al.* J Biochem 1995 270:1048-56). *Perez-Paya et al* teach "MINOR MODIFICATIONS IN THE AMINO ACID SEQUENCE OF MELITTIN RESULT IN DRAMATIC CHANGES IN ITS BIOLOGICAL ACTIVITY." (Biochem J 1994) "AMPHIPATHIC α-HELICES WERE FOUND TO BE A KEY DETERMINING FEATURE IN THE EARLY FOLDING PROCESS OF THE SELF ASSOCIATION OF PEPTIDES AND PROTEIN SEGMENTS. THOSE SUBSTITUTIONS, WHICH PREVENTED THE INDUCIBLE AMPHIPATHIC FOLDING ABILITY, WERE ALSO FOUND TO RESULT IN A LOSS IN HEMOLYTIC AND ANTIMICROBIAL ACTIVITY." (J Biochem 1995). *Jaynes et al* (U.S. 6,255,282) teach, that changes in either end of the amino acid sequence of naturally occurring cecropin (analogs) generally results in losses in bactericidal activity in varying degrees against different bacteria. According to above teachings, the antimicrobial activity of melittin and cecropin analogues will vary significantly depending on changes in the position and substitution of amino acid residues. It would have required undue experimentation for the skilled artisan intending

to practice the invention to determining what kind of analogues would meet claim limitation.

With respect to the homologues, the specification fails to specifically define the term. Accordingly, the claims encompass any peptide bearing any degree of homology with the melittin or cecropin. The specification teaches the cecropin B analogue Shiva-1, which bears about 40% sequence homology, and maintains the same charge distribution and hydrophobicity as the peptide (Specification, page 4, lines 7-10). On the other hand, other cited art teaches that just one or a few deletions may lead to the loss of the bactericidal activity (e.g. *Jaynes et al)*. It would have required undue experimentation for the skilled artisan intending to practice the invention to search through a large number of peptides that share any degree of sequence homology with melittin and cecropin to find the biologically active derivatives.

In the response filed 8/30/03, Applicants argue that claims are not drawn to any AMP, had been amended to limit to melittins and cecropins, deletions of melittin and SB-47 and Shiva-1 (analog of cecropin) have been described in the specification, and claims 53, 54, 57, and 58 are directed to these specific analogues. Applicants go on to argue that methods of obtaining a biologically active derivative is known to those of skill in the art, and a substantial amount of information in this field of art is readily available for making and assessing analogues or homologues of an antimicrobial peptide.

The argument has been carefully considered, but found not persuasive. Because the base claims are much broader than the specific analogs, claims 53 and 54 have been canceled, and claims 57 and 58 are not drawn to any particular analog or homologue.

Accordingly for the reasons of record and those set forth above, the specification fails to meet the written description provision of 35 U.S.C. §112, first paragraph.

ENABLEMENT REQUIREMENT

To the extent that the claimed vectors are not adequately described in the instant disclosure, claims 1, 2, 4-15, 20-22, 26-28, 30, 31, 34-40, 46-48, 52, 55-65, 70-72, 75 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been adequately described.

Considering the level of the skill and state of the art taught by *Boman, Perez-Paya, Rivitte et al*, and *Jaynes et al*, without actual experimental evaluation, the results of making and using fragments, homologs, and analogs will be highly unpredictable. The specification is not sufficient to enable one skill in the art making and using the invention to its full scope, the skilled artisan intending to practice the invention could not do so without undue experimentation.

Accordingly, for reasons of record and those set forth above, the instant specification fails to meet the enablement requirement.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4-15, 20-22, 26-28, 30, 31, 34-40, 46-48, 52, 55-65, 70-72, 75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because of the claim recitation, "a biologically active derivative", "a part thereof, an analogue thereof, and a homologue thereof". This is because the lower limits of the part and the homologue have not been specified, the extent of variation of an analogue is not specified. Further, the specification fails to teach how to determine whether a peptide is derived from melittin or cecropin, it is unclear what is encompassed or excluded by these terms, thus the metes and bounds of the claims could not be readily determined.

With respect to the claim recitation, "a biologically active derivative" of melittin and cecropin, since they possess many different biological activities in addition to bactericidal activity, such as the activity of stimulating lymphocyte proliferation as taught by *Jaynes et al* (US 5,962,410, e.g. abstract), it is unclear which activity the term refers to and how to determine the derivatives having the recited property, thus the metes and bounds of the claims cannot be readily determined.

Claims 12, 38, 63 recite the limitation, "the U3 sequence". There is insufficient antecedent basis for this limitation in the claims.

Claims 13, 39, 64 recite the limitation "said polylinker". There is insufficient antecedent basis for this limitation in the claim.

Claims 21 and 71 are vague and indefinite because of the claim recitation, "a RNA produced by a vector", wherein the vector is a retroviral vector DNA. It is unclear how a DNA vector produces a RNA, thus, the metes and bounds of the claims are uncertain.

Claim Objections

Claim 47 is objected to because the word "vector" before the "recombinant" should be deleted.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 9, 11, 14, 15, 20, 21, 22, 26, 27, 35, 37, 40, 46, 47, 48, 52 are rejected under 35 U.S.C. 102(e) as being anticipated by *Curiel et al* (US 6,022,735).

Curiel et al teach a retroviral DNA vector (pCMVL, column 35, § b) and packaging cells (column 36, § b), wherein the vector encoding and expressing melittin (table 3), and method of transfecting BNL CL.2 cells, whereby RNA would be produced by these cells. Accordingly, *Curiel et al* anticipate instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-15, 20-22, 26-28, 30, 31, 34-40, 46-48, 52, 55-65, 70-72, 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Jaynes et al* (US 5,962,410), in view of *Gilboa et al* (US 5,658,775) and *Hodgson et al* (US 6,027,722).

Jaynes et al teach lytic peptides such as the cecropin and melittin and using such for inhibition of eukaryotic pathogens and neoplasmic cells (e.g. abstract and example 4). They go on to teach that lytic peptides could also be delivered via retroviral vector encoding the peptide to cells of interest (column 12, lines 50-58). *Jaynes et al* do not detail how the retroviral expression vector is constructed.

Gilboa et al teach constructing a retrovial vector (retroviral vector DNA) for producing foreign gene product in animal cells, wherein the vector comprising at least a portion of retrovirus including both the 5' retroviral LTR region and 3' LTR region

containing the U3-R-U5 structure, wherein the foreign gene to be expressed is inserted in the U3 region of 3' LTR (fig. 4), wherein a polylinker cloning site is present (column 6, line 48), wherein a promoter sequence such as VIP is also present. *Gilboa et al* also teach a recombinant retroviral vector system for producing a virion and using the virion transfecting a target cell (fig. 1), such as NIH3T3 and human lymphoid cells (animal and human cells, column 11, lines 21-23). *Gilboa et al* do not teach expressing the lytic peptides or complete deletion of U3 region.

Hodgson et al teach a 5' long terminal repeat region (LTR) comprising the U3-R-U5 structure and a 3' LTR comprising the U3-R-U5 structure, wherein the U3 is partially or completely deleted and replaced with a sequence which comprises at least one unique restriction site (fig 2a) and at least one insertion of a heterologous DNA fragment operably linked to a promoter (figs. 4, 5). They teach the strategy of inserting foreign gene at the 3'LTR region, wherein a large deletion occurred in the U3 region and replaced by a cloning site comprising at least one unique restriction site (column 21, § 11, particularly column 21, line 67-column 22, line 4), wherein a transacting molecule (P4) could be included for regulating foreign gene expression (fig. 14)

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the retroviral vectors taught by *Gilboa et al*, and *Hodgson et al et al*, in the method of *Jaynes et al* for expressing a lytic peptide in animal cells with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because given the numerous retroviral vectors known in the art, it is within the levels of the reasonably skilled to use an

appropriate vector for expressing a gene of interest. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is **703-308-0196**.

JANICE LI
PATENT EXAMINER

Q. Janice Li
Patent Examiner
Art Unit 1632

QJL
February 23, 2004